Synthesis of an Enantiopure *syn*-Benzocyclotrimer through Regio-selective Cyclotrimerization of a Halonorbornene Derivative under Palladium Nanocluster Conditions

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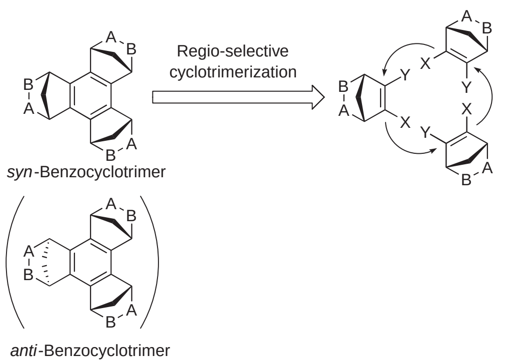
An enantiopure *syn*-benzocyclotrimer **1** was selectively synthesized from an enantiopure halonorbornene **2** through regioselective cyclotrimerization catalyzed by palladium nanoclusters. The yield of **1** was dependent on the stability of the palladium clusters, which was ascertained from the appearance and TEM images of the reaction mixtures. The thus-prepared enantiopure benzocyclotrimer will serve as a key intermediate for the synthesis of C_{3v} symmetric chiral buckybowls.

Benzocyclotrimers of bicycloalkenes have been of interest due to characteristic features including bond alternation of the benzene ring, unusual electronic properties, and their C_{3v} symmetric cup-shaped structure, which would be suitable for molecular recognition.[1–4] A recent report showed that a *syn*-benzocyclotrimer of norbornadiene could serve as a key intermediate in the synthesis of a C_{3v} symmetric buckybowl, sumanene.[5] According to this synthetic strategy, a variety of *syn*-benzocyclotrimers of norbornene derivatives can be utilized as the precursors for highly functionalized C_{3v} symmetric buckybowls including chiral buckybowls. Here, we report the syn-selective synthesis of an enantiopure benzocyclotrimer **1** from an enantiopure halonorbornene derivative **2** through regio-selective cyclotrimerization under palladium nanocluster conditions.

In general, the cyclotrimerization of norbornene derivatives affords a mixture of *syn*- and *anti*-benzocyclotrimers, where the *anti*-benzocyclotrimers are usually predominant.[6–8] To achieve the syn-selective preparation, the use of enantiopure norbornene derivatives ($X \neq Y$) and regio-selective cyclotrimerization are preferable (Scheme 1).[7] Among several coupling partners, halonorbornene derivatives (X = halogen, Y = H) seem the most suitable candidates as starting materials because their enantiomers are easily accessible. However, although cyclotrimerization of racemic halonorbornenes has been carried out using Pd catalyst ($Pd(OAc)_2$, PPh_3, Bu_4NBr, NEt_3, MS 4 Å, 80 °C in DMF) it was the *anti*-benzocyclotrimers that were obtained selectively. Indeed, this method could not be applied to syn-selective cyclotrimerization from enantiopure derivatives.[8]

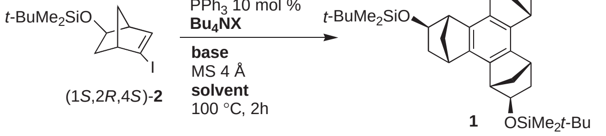
The cyclotrimerization of an enantiopure halonorbornene derivative (1*S*,2*R*,4*S*)-**2**[9] was chosen as our target because the product *syn*-**1** is expected to be a common synthetic intermediate in construction of C_{3v} symmetric chiral buckybowls. The cyclotrimerization of **2** under the reported conditions[8] did not take place, giving a complex mixture with only a trace amount of *syn*-**1** as reported (Table 1, Entry 1). After screening several conditions, we found that the desired *syn*-**1** was obtained in 34% yield as a single isomer when using Bu_4NOAc and Na_2CO_3 in 1,4-dioxane solution (Table 1, Entry 2). In particular, the addition of Bu_4NOAc was crucial for the reaction.[10] The yield of **1** was dependent on the amount of Bu_4NOAc, indicating that the Pd nanoclusters generated in the reaction mixture might play an important role (vide infra). That is, the yield was improved to 53% by increasing the amount of Bu_4NOAc to 1000 mol % (Table 1, Entry 2–5).

Photographs and typical TEM images of the reaction mixtures under the conditions listed in Entries 1, 2, 4, and 5 in Table 1 are shown in Figure 1. Judging from the appearance of the reaction mixtures, the Pd nanoclusters were well dispersed in the order of (B) < (C) < (D) which was consistent with the amount of Bu_4NOAc. The amount of precipitation of Pd black was observed in the opposite order, (B) > (C) > (D). The TEM images supported these observations. In Table 1, we show the result using the conditions reported in a previous paper,[8] which are considered typical reaction conditions for generation of Pd nanoclusters (Entry 1; Figure 1A). Indeed, the appearance



Scheme 1. Synthesis of enantiopure *syn*-benzocyclotrimers through regio-selective cyclotrimerization of enantiopure norbornene derivatives.

Table 1. Palladium-catalyzed cyclotrimerization of the enantiopure **2**.



Entry	Bu_4NX		Base		Solvent	Yield of $\mathbf{1}^a$/%
1[b]	Bu_4NBr	100 mol %	NEt_3	250 mol %	DMF	trace
2	Bu_4NOAc	100 mol %	Na_2CO_3	1000 mol %	1,4-dioxane	34
3	Bu_4NOAc	300 mol %	Na_2CO_3	1000 mol %	1,4-dioxane	42
4	Bu_4NOAc	500 mol %	Na_2CO_3	1000 mol %	1,4-dioxane	47
5	Bu_4NOAc	1000 mol %	Na_2CO_3	1000 mol %	1,4-dioxane	53

[a]Isolated yield. [b]Reported conditions in Ref. 8.

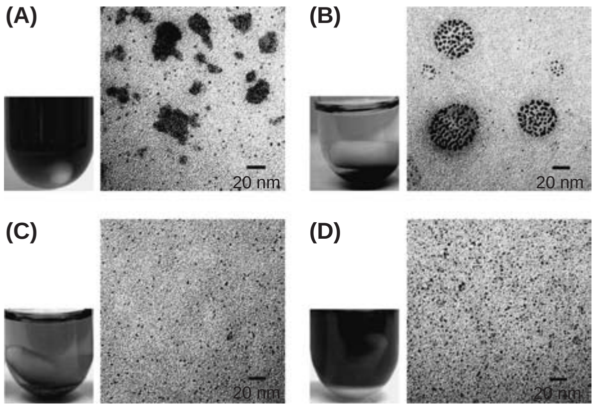
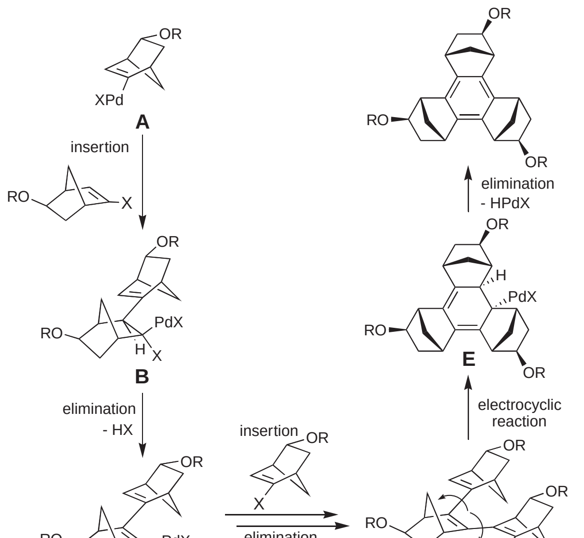


Figure 1. Photographs and typical TEM images of the reaction mixtures; (A) Entry 1, (B) Entry 2, (C) Entry 4, and (D) Entry 5 in Table 1.

of (A) was similar to that of (D), indicating the formation of nanoclusters. However, a considerable degree of aggregation of clusters was observed in the TEM images as well as in those of (B). Although both clusters in (C) and (D) were well dispersed judging from the TEM images, the concentration of clusters was much higher in (D), consistent with their appearance. These observations strongly suggest that the generation of Pd nanoclusters in appropriate conditions might be very important and that an excess amount of Bu_4NOAc could realize well-dispersed nanoclusters.[11]

A possible mechanism of the cyclotrimerization is shown in Scheme 2.[8a] Halonorbornene **2** oxidatively added to the Pd^0 species generated from the Pd nanoclusters to afford the intermediate **A**. Insertion of another **2** to **A** proceeded regio-selectively,[12] giving the Pd carbenoid **B**. Due to its carbenoid character, the formal syn elimination of HX might take place smoothly, leading to the dimeric vinyl Pd intermediate **C**. After another repetition of this process, the thus-obtained trimer complex **D** underwent electrocyclization to afford **E**, from which spontaneous syn elimination of HPdX and aromatization occurred. The role of the Pd nanoclusters in the process might be understood in relation to the mechanistic insight of the Heck reaction. For the Heck reaction, atomic palladiums leached from nanoclusters were reported to be the active species.[13] Since there are two Heck-type insertion steps at sterically hindered positions, the present reaction might be controlled by the active Pd species continuously leached from the high concentrated Pd nanoclusters.



Scheme 2. A possible reaction pathway (R = $SiMe_2t$-Bu).

As described above, **1** was successfully synthesized as an enantiopure form through regio-selective cyclotrimerization under palladium nanocluster conditions. The thus-prepared enantiopure benzocyclotrimer will serve as a key intermediate for the syntheses of C_{3v} symmetric chiral buckybowls. In addition, the information about the stability of Pd nanoclusters would be applicable to other reactions.

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References and Notes

1 a) N. L. Frank, K. K. Baldridge, J. S. Siegel, *J. Am. Chem. Soc.* **1995**, *117*, 2102. b) A. Matsuura, K. Komatsu, *J. Am. Chem. Soc.* **2001**, *123*, 1768.

2 a) P. G. Gassman, I. Gennick, *J. Am. Chem. Soc.* **1980**, *102*, 6863. b) N. L. Frank, K. K. Baldridge, P. Gantzel, J. S. Siegel, *Tetrahedron Lett.* **1995**, *36*, 4389. c) R. Rathore, S. V. Lindeman, A. S. Kumar, J. K. Kochi, *J. Am. Chem. Soc.* **1998**, *120*, 6012.

3 a) H. Hart, S. Shamouilian, Y. Takehira, *J. Org. Chem.* **1981**, *46*, 4427. b) K. Komatsu, H. Akamatsu, Y. Jinbu, K. Okamoto, *J. Am. Chem. Soc.* **1988**, *110*, 633.

4 C. Zonta, S. Cossu, O. De Lucchi, *Eur. J. Org. Chem.* **2000**, 1965.

5 H. Sakurai, T. Daiko, T. Hirao, *Science* **2003**, *301*, 1878.

6 a) R. Durr, O. De Lucchi, S. Cossu, V. Lucchini, *Chem. Commun.* **1996**, 2447. b) C. Zonta, S. Cossu, P. Peluso, O. De Lucchi, *Tetrahedron Lett.* **1999**, *40*, 8185. c) A. Paulon, S. Cossu, O. De Lucchi, C. Zonta, *Chem. Commun.* **2000**, 1837. d) F. Fabris, L. Zambrini, E. Rosso, O. De Lucchi, *Eur. J. Org. Chem.* **2004**, 3313.

7 a) S. Cossu, C. Cimenti, P. Peluso, A. Paulon, O. De Lucchi, *Angew. Chem., Int. Ed.* **2001**, *40*, 4086. b) F. Fabris, L. Bellotto, O. De Lucchi, *Tetrahedron Lett.* **2003**, *44*, 1211.

8 a) S. Cossu, O. De Lucchi, A. Paulon, P. Peluso, C. Zonta, *Tetrahedron Lett.* **2001**, *42*, 3515. b) L. Zambrini, F. Fabris, O. De Lucchi, G. Gardenal, F. Visentin, L. Canovese, *Tetrahedron* **2001**, *57*, 8719.

9 (1*S*,2*R*,4*S*)-**2** (>99% ee) was prepared from (1*S*,2*R*,4*S*,5*R*)-norbornane-2,4-diol.[14] For the preparation of (1*S*,2*R*,4*S*,5*R*)-norbornane-2,4-diol, see the following references: a) T. Hayashi, Y. Uozumi, *Pure Appl. Chem.* **1992**, *64*, 1911. b) A. Berkessel, M. Schroder, C. A. Sklorz, S. Tabanella, N. Vogl, J. Lex, J. Neudorfl, *J. Org. Chem.* **2004**, *69*, 3050.

10 Choice of solvent and base was also essential to improve the yield. Details of such effects will be discussed elsewhere.

11 I. Quiros, M. Yamada, K. Kubo, J. Mizutani, M. Kurihara, H. Nishihara, *Langmuir* **2002**, *18*, 1413.

12 R. J. Deeth, A. Smith, J. M. Brown, *J. Am. Chem. Soc.* **2004**, *126*, 7144.

13 M. B. Thathagar, J. E. ten Elshof, G. Rothenberg, *Angew. Chem., Int. Ed.* **2006**, *45*, 2886, and references cited therein.

14 Supporting Information is also available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

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